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(54) Title: PREPARATION OF BIARYL COMPOUNDS

(57) Abstract

A method for the preparation of biaryl compounds is disclosed which comprises contacting an aromatic halide in the presence of a catalyst comprising zerovalent nickel, a bidentate phosphorus-containing coordinating ligand and a reducing metal in a polar, aprotic solvent system for a time and under conditions suitable for the formation of biaryl compound.

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Description  
PREPARATION OF BIARYL COMPOUNDS

This application is a continuation-in-part of  
5 Serial No. 277,826, filed November 30, 1988, now  
pending.

The present invention relates to the preparation of  
biaryl compounds from aryl halides. In a particular  
aspect, the present invention relates to the reductive  
10 coupling of aryl halides.

Background of the Invention

It is known that biphenyl compounds can be produced  
by the reductive coupling of aryl halides. For example,  
15 Chao, et al., in the Journal of Organic Chemistry,  
Volume 48, at pages 4904-4907 (1983), disclose the  
reaction of aryl halides with an equivalent amount of a  
highly activated metal such as nickel powder.

An alternative approach is to activate an aryl  
20 halide by a chemical transformation, and then allow the  
activated aryl halides to couple to form biaryl species.  
For example, Gilman, et al., in the Journal of the  
American Chemical Society, Volume 61, at pages 957-959  
(1939), demonstrated this approach by the reaction of  
25 two equivalents of aryl Grignard reagents with one  
equivalent of nickel(II) salts to give biaryl compounds.  
This reaction is believed to proceed through the  
bis(aryl)nickel(0) species which then decomposes to give  
the desired biaryl product.

30 Kumada, et al., in Bulletin of the Chemical Society  
of Japan, Volume 49, at pages 1958-1969 (1976), have  
demonstrated that aryl halides can be reacted with a  
variety of aliphatic Grignard reagents to give alka-aryl  
products. However, attempts to couple aryl Grignard  
35 reagents with aryl halides were successful only with

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aryl bromides. Attempts to use aryl chlorides gave less than a ten percent yield of desired biaryl products.

Aryl chlorides are frequently more readily available than are the corresponding bromides and 5 iodides. The chlorides are also typically less reactive and are less expensive materials as well. It would, therefore, be desirable to find a means to promote the coupling of aryl chlorides to produce high yields of biaryl compounds.

10 Such coupling of aryl chlorides has been disclosed by Colon, et al., in U.S. 4,263,466. The authors disclose the use of a metallic reducing agent such as zinc, magnesium, or manganese in a dipolar, aprotic solvent such as dimethylformamide with a catalyst 15 containing a nickel compound in combination with triaryl organophosphines and alkali metal halide promoters. The reducing metal converts the nickel salts into highly reactive zerovalent nickel compounds which promote the coupling of the aryl halides and regenerate the nickel 20 salts which can be reduced again to the zerovalent state, thereby maintaining the catalytic cycle.

In later publications by the same authors (see Colon, et al., in Journal of Organic Chemistry, Vol. 51 at pages 2627-2637 (1986), it is indicated that 25 bidentate ligands (as opposed to the monodentate triaryl organophosphines disclosed in '466) are not effective for the nickel/reducing metal-promoted reductive coupling reaction. Takagi, et al., in the Bulletin of the Chemical Society of Japan, at 30 pages 1887-1890 (1984) have made similar observations. See especially Run Number 14 reported at page 1888.

#### Statement of the Invention

In accordance with the present invention, it has 35 surprisingly been found that aryl chlorides can be

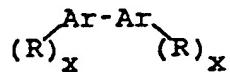
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reductively coupled employing bidentate ligands to produce biaryl compounds in high yield. By contacting aryl halides with a catalyst comprising a nickel compound, at least one bidentate phosphorus-containing 5 ligand selected from a specified group and a reducing metal, high yields of biaryl compounds are obtained.

The practice of the present invention allows for the ready preparation of biaryl derivatives from aryl chloride starting materials. Aryl chlorides are 10 generally preferred starting materials as they are more accessible on a commercial basis and are generally less expensive than the corresponding aryl bromides or aryl iodides.

15 Detailed Description of the Invention

In accordance with the present invention, there is provided a method for the preparation of biaryl compounds of the structure:

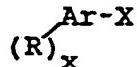


20 wherein Ar is an aromatic moiety having in the range of 4 up to 20 carbon atoms, each R is independently 25 selected from alkyl, aryl, -F, -NR'₂, -CN, -CHO, -OR', -OCO-R', -COO-R', -C<sup>O</sup>-R', -SO<sub>2</sub>-R', -SO<sub>3</sub>R', or 35 -NR'COR':

40 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms, and x is an integer falling in the range of 0 up to 8, depending on the size 45 of the aromatic ring, Ar, and with the proviso that there be no more than one substituent ortho to the Ar-Ar bond.

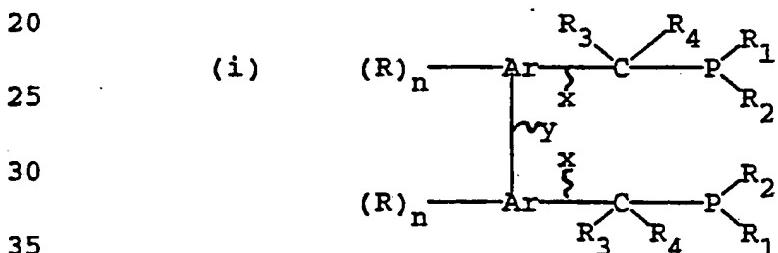
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The invention method comprises contacting an aromatic halide having the structure:



wherein Ar, R and x are as defined above and X is a halogen; under conditions suitable for the formation of the desired biaryl compound in the presence of at least 0.001 equivalents of a nickel catalyst comprising:

- 15 I) an anhydrous nickel compound,
- II) at least one bidentate phosphorus-containing ligand selected from the group consisting of:



40 wherein each Ar is independently selected from aromatic ring compounds having 6 up to 14 carbon atoms, e.g., phenyl, naphthyl, phenanthryl or anthracenyl;

45 the x bonds and the y bonds are attached to adjacent carbon atoms on the ring structures;

- 5 -

- each R, when present as a substituent, is independently selected from alkyl, aryl, -F, -NR'<sub>2</sub>, -CN, -CHO, -OR', -OCO-R',  
5 -COO-R', -C<sup>O</sup>-R', -SO<sub>2</sub>-R', -SO<sub>3</sub>-R', or  
-NR'COR':  
10 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms;  
15  
n is a whole number in the range of 0-4 where Ar is phenyl; 0-6 where Ar is naphthyl; and 0-8 where Ar is phenanthryl or  
20 anthracenyl;
- each R<sub>1</sub> and R<sub>2</sub> is independently selected from alkyl, aryl, aralkyl, alkaryl or cycloaliphatic radicals, or substituted derivatives thereof wherein substituted derivatives include ethers, amines, amides, sulfonic acids, esters, hydroxyl groups and alkoxy groups;  
25  
each R<sub>3</sub> and R<sub>4</sub> is independently selected from hydrogen and the R<sub>1</sub> substituents;  
30 each of the above alkyl groups or moieties is straight or branched chain of 1-20 carbons;  
35 each aryl group contains 4-20 ring carbons; and  
40 each cycloaliphatic group contains from 4-8 ring carbons;

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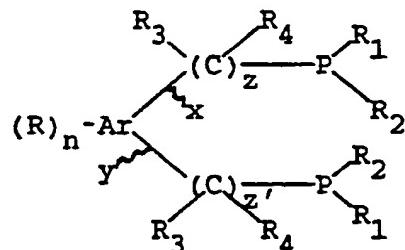
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(ii)

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wherein Ar, x, y, R, n, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are each as defined above, and each of z and z' can independently vary between 0 and 4, with the proviso that z+z' is at least 2;

25

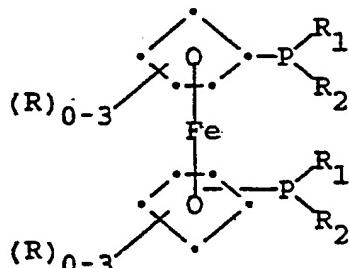
(iii)

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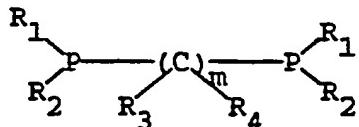


wherein R, R<sub>1</sub>, and R<sub>2</sub> are as defined above; and

50

(iv)

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60

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as defined above; and m is a whole number which can vary from 4 up to 8; preferably from 5 up to 8;

65

as well as mixtures of any two or more of said type (i), (ii), (iii), or (iv) organophosphines; and

III) at least one reducing metal selected from

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the group consisting of zinc, magnesium and manganese,

wherein said contacting is carried out in a  
polar, aprotic, solvent system for a time  
and under conditions suitable for the  
formation of the desired biaryl compound.

Reaction temperatures employed in the practice of the present invention can vary widely. Typically, reaction temperatures fall in the range of about 0 up to 250°C, with reaction temperatures in the range of about 25 up to 120°C being preferred.

Reaction times contemplated for the practice of  
the present invention can vary widely. One of skill in  
the art can readily determine that amount of time which  
is sufficient to allow formation of the desired biaryl  
or heterobiaryl compounds. Typically, reaction times  
will fall in the range of about 0.1 up to 24 hours or  
longer, with reaction times in the range of about 0.5 up  
to 16 hours being preferred.

Aryl halides contemplated for use in the practice of the present invention are compounds have the general structure:

25 Ar-X  
(R)<sub>x</sub>

30 wherein Ar is an aromatic moiety having in the range of  
 4 up to 20 carbon atoms, each R is independently  
 selected from alkyl, aryl, -F, -NR'<sub>2</sub>, -CN, -CHO,  
 35 -OR', -OCO-R', -C<sup>O</sup>-R', -SO<sub>2</sub>R', SO<sub>3</sub>R', or NR'COR':

40 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms; X is a halogen and x is an integer falling in the range of 0 up to 8, depending on the size of the aromatic ring, Ar, and with the further

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proviso that there be no more than one substituent ortho to the halogen moiety. Exemplary aryl halides contemplated for use in the practice of the present invention include:

- 5            2-chlorotoluene,  
              2-bromotoluene,  
              4-chlorotoluene,  
              4-bromotoluene,  
              2-chloro-4-methylnaphthalene,  
10            2-bromo-4-methylnaphthalene,  
              4-chloroanisole,  
              4-bromoanisole,  
              4-chlorophenylacetate,  
              4-bromophenylacetate,  
15            2-chlorobenzyl(2-methoxy)ethyl ether,  
              2-bromobenzyl(2-methoxy)ethyl ether,  
              2-chlorobenzyl methyl ether,  
              2-bromobenzyl methyl ether,  
              2-chlorobenzyl ethyl ether,  
20            2-bromobenzyl ethyl ether,  
              2-chlorothiophene,  
              2-bromothiophene,  
              2-chloropyridine,  
              2-bromopyridine,  
25            2-chloro-3-methylnaphthalene,  
              2-bromo-3-methylnaphthalene,  
              1-chloro-2-methylnaphthalene,  
              1-bromo-2-methylnaphthalene,  
              1-methyl-2-chloronaphthalene,  
30            1-methyl-2-bromonaphthalene,  
              4-fluoro-2-chlorotoluene,  
              4-fluoro-2-bromotoluene,  
              4-(N-ethyl-N-acetyl)-2-chlorotoluene,  
              4-(N-ethyl-N-acetyl)-2-bromotoluene,

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6-(N-ethyl-N-acetyl)-2-chlorotoluene,  
6-(N-ethyl-N-acetyl)-2-bromotoluene,  
and the like; as well as mixtures of any two or more  
thereof.

5 Presently preferred monohalides contemplated for  
use in the practice of the present invention include  
compounds having the structural formula:

10

15

20



(I)

wherein one or more of the carbon atoms of the  
benzene ring in formula (I) is optionally replaced by N;

25 wherein X is a halogen selected from the group  
consisting of Cl, Br and I;

30 R is a monovalent radical selected from alkyl,  
aryl, -F, -NR'<sub>2</sub>, -CN, -CHO, -OR', -OCO-R, -COO-R',  
-C<sup>O</sup>-R', -SO<sub>2</sub>-R', -SO<sub>3</sub>-R', or -NR'COR':

35 wherein R' is a hydrocarbyl or heteroaryl radical  
having up to 20 carbon atoms, and x is an integer having  
values of 0 to 4 with the proviso that no more than one  
R is in a position ortho to the X-containing ring carbon  
atom.

40 Additional compounds contemplated by the above  
structural formula are those wherein one or more of the  
carbon atoms of the benzene ring is replaced by N.  
Especially preferred compounds contemplated by the above  
formula are those wherein X is Cl.

45 Examples of preferred monohalides which satisfy  
structural formula (I) include:

2-chlorotoluene,  
2-chloropyridine,  
4-fluoro-2-chlorotoluene,

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2-chlorobenzyl methyl ether,  
2-chlorobenzyl ethyl ether,  
4-(N-ethyl-N-acetyl)-2-chlorotoluene,  
6-(N-ethyl-N-acetyl)-2-chlorotoluene,

5           4-chlorotoluene,  
4-chloroanisole,

2-chlorobenzyl(2-methoxy)ethyl ether,  
as well as mixtures of any two or more thereof.

A wide range of nickel compounds are suitable for  
10       use in the practice of the present invention, so long  
as the nickel compounds employed are essentially  
water-free. The nickel(II) halide salts are a  
convenient source of nickel as such compounds are  
readily available in anhydrous form. Alternatively,  
15       hydrates of such compounds can be employed if an  
appropriate means of water removal, e.g., azeotropic  
distillation, is employed prior to contacting the  
nickel species with the reducing metal and aryl halide.  
Those of skill in the art recognize that a wide variety  
20       of nickel compounds can be used in addition to the  
nickel(II) halides, e.g., nickel nitrates, sulfates,  
phosphates, oxides, carbonates, carboxylates,  
acetylacetone and the like, as well as Ni(0) complexes  
such as, for example, bis(1,5-cyclooctadienyl)nickel(0),  
25       nickel(0) tetracarbonyl, and the like.

The nickel(II) halides are presently preferred  
because of their ready availability in anhydrous form  
(or, alternatively, the ease with which the hydrates  
form such compounds can be dehydrated), and because the  
30       presence of halides in the reaction mixture appears to  
promote the coupling reaction. Especially preferred are  
nickel chloride and nickel bromide.

Suitable ratios of nickel to aryl halides can  
vary widely. Molar ratios in the range of 0.0001 up to  
35       0.5:1 are generally suitable. Ratios in the range of

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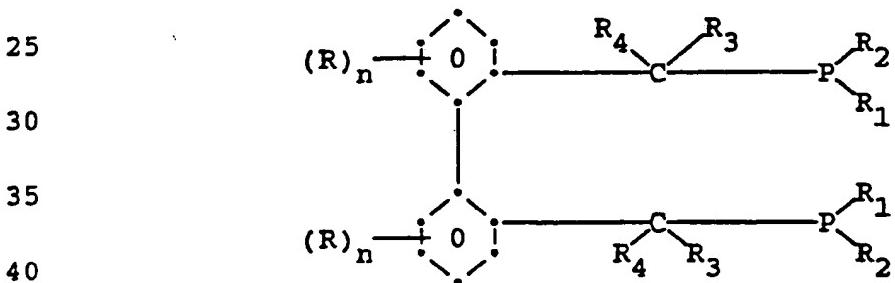
about 0.01 up to 0.2:1 are preferred, with molar ratios in the range of about 0.03 up to 0.1 being most preferred because good conversions are obtained at reasonable reaction rates.

5        Optionally added to the catalyst composition are inorganic salt promoters. When used, preferred promoters include alkali, alkaline earth, zinc, magnesium, manganese and aluminum halides, or mixtures thereof. Bromides are particularly preferred. The  
10      amount of promoter, when used, can range from about 0.1 to about 1000 moles per gram atom of nickel with about 1 to about 100 moles of promoter being preferred.

15      The presently most preferred promoters include alkali metal iodides, alkali metal bromides and alkali metal chlorides.

Organophosphines contemplated for use in the practice of the present invention are compounds having the structures set forth above as (i), (ii), (iii), or (iv).

20      Exemplary compounds contemplated by structure (i) include compounds having the structural formula:



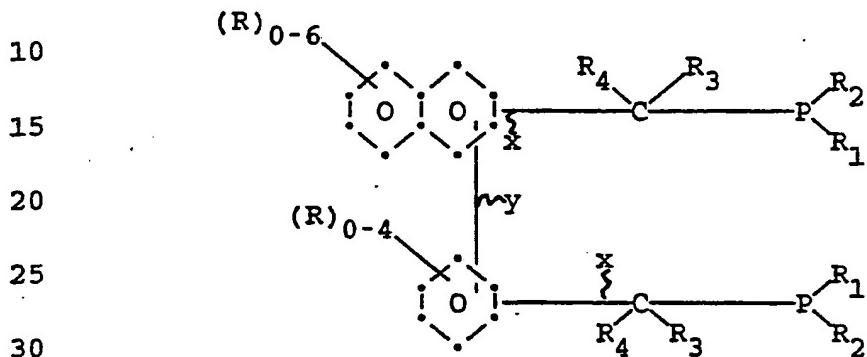
45      wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and n are as defined above; including such compounds as

2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl;  
2,2'-bis(dibenzylphosphinomethyl)-1,1'-biphenyl;

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2,2'-bis(phenylbenzylphosphinomethyl)-1,1'-biphenyl; and  
2,2'-bis(diisobutylphosphinomethyl)-1,1'-biphenyl.

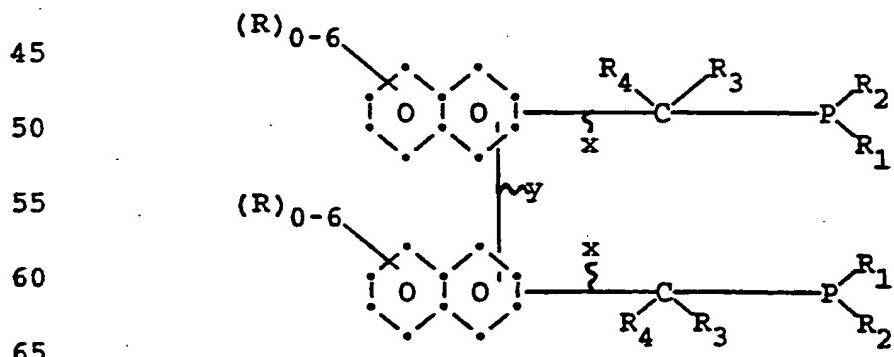
5 Exemplary compounds contemplated by structure (i)  
also include compounds having the structural formula:



10 wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, x and y are defined  
15 above; such as, for example

2-(diphenylphosphinomethyl)-1-[2-(diphenylphosphino-methyl)phenyl]naphthalene.

20 Exemplary compounds contemplated by structure (i)  
also include compounds having the structural formula:

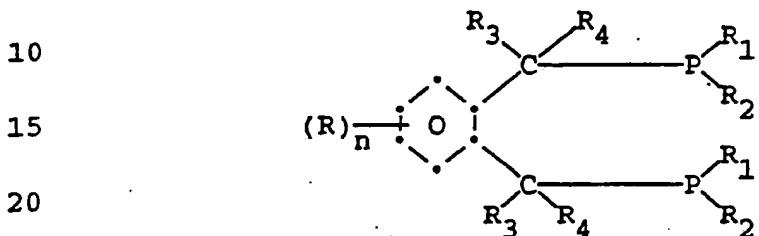


25 wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, x and y are as defined  
30 above; such as, for example

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**2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl.**

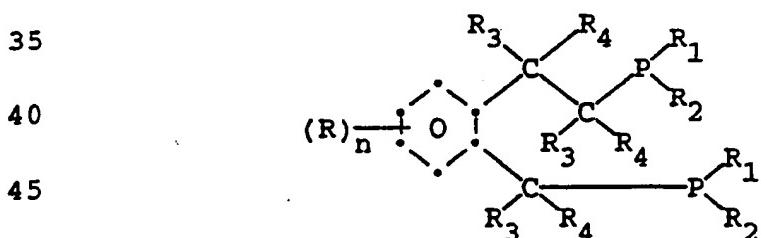
5           **Exemplary compounds contemplated by structure  
(ii) include compounds having the structural formula:**



wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and n are as defined above; such as, for example

$\alpha,\alpha'$ -bis(diphenylphosphino)ortho-xylene.

30           **Exemplary compounds contemplated by structure (ii)  
also include compounds having the structural formula:**

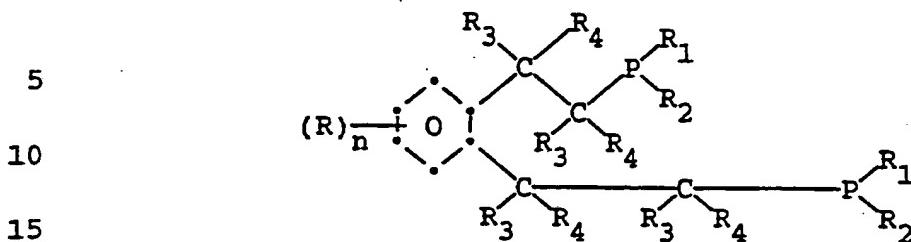


wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and n are as defined above; such as, for example

55            $\alpha,\beta'$ -bis(diphenylphosphino)-2-ethyltoluene.

**Exemplary compounds contemplated by structure (ii)  
also include compounds having**

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wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and n are as defined above; such as, for example

1,2-bis[2-(diphenylphosphino)ethyl]benzene.

Exemplary compounds contemplated by structure

25 (iii) include: 1,1'-bis(diphenylphosphino)ferrocene, and the like.

Exemplary compounds contemplated by structure

(iv) include:

30 1,4-bis(diphenylphosphino)butane,

1,5-bis(diphenylphosphino)pentane, and

35 1,6-bis(diphenylphosphino)hexane;

as well as mixtures of any two or more thereof. Also contemplated are mixtures of any two or more of said 40 type (i), (ii), (iii) or (iv) organophosphines.

The molar ratio of organophosphine to nickel compound employed in the practice of the present invention can vary widely. Typically, such molar ratio will fall within the range of 0.5:1 up to 20:1, with 45 ratios in the range of 1:1 up to 10:1 preferred. Ratios in the range of about 1:1 up to 3:1 are presently most preferred because little added benefit is seen in the use of large excesses of organophosphine(s).

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Optional coordinating ligands employed in combination with the above-described bidentate organophosphines are bidentate ligands containing at least one nitrogen atom as part of an aromatic ring structure. Such bidentate ligands include bipyridine, a C<sub>1</sub> up to C<sub>6</sub> dialkylamino pyridine, phenanthroline or 2-picolinic acid, and the like.

When the optional use of mixtures of bidentate organophosphine and bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure are employed as the coordinating ligand, molar ratios of the bidentate organophosphine to the bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure can vary widely, for example, in the range of about 0.1:1 up to 20:1, with ratios in the range of 0.5 up to 10 preferred. Ratios in the range of about 1:1 up to 2:1 are presently most preferred because little added benefit is observed when large excesses of the bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure are employed.

Solvents suitable for use in the practice of the present invention include dipolar, aprotic solvents such as solvents, such as N,N-dimethylacetamide, N,N-dimethylformamide, 1-methyl-2-pyrrolidinone, tetramethylurea, dimethylsulfoxide, sulfolane, and the like. If desired these dipolar, aprotic solvents can be mixed with lower polarity inert solvents, such as saturated aliphatic hydrocarbons, including pentanes, hexanes, dodecane and the like; aromatic hydrocarbons, such as benzene, toluene, xylenes and the like; and saturated aliphatic and cycloaliphatic ethers, such as, diethyl ether, diglyme, tetrahydrofuran and the like.

It is preferred that all solvents used in the practice of this invention be anhydrous.

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Although magnesium and manganese metals can be used, zinc metal is the presently preferred reducing metal for use in the invention process for coupling aryl monochlorides.

5       The molar ratio of reducing metal to aryl halide employed in the practice of the present invention can vary widely. Typically, such molar ratio will fall within the range of about 0.01:1 up to 20:1, with ratios in the range of about 0.2:1 up to 10:1  
10      preferred. Ratios in the range of about 0.4:1 up to 5:1 are presently most preferred because it is desired to minimize the quantity of reducing metal which must be removed from the reaction mixture and little added benefit is obtained when large excesses of reducing  
15      metal are employed.

The molar ratio of reducing metal to nickel employed in the practice of the present invention can vary widely. Typically, such molar ratios will fall within the range of about 1 up to 1000:1, with ratios  
20      in the range of about 10 up to 500:1 being preferred. Ratios in the range of about 40 up to 100:1 are presently preferred for the same reasons as stated in the preceding paragraph.

25      Preparation of the novel catalyst composition is carried out conveniently by mixing the aforementioned nickel compound, ligand(s), promoter, and reducing metal(s) in the dipolar, aprotic solvent under an inert atmosphere and heating to a temperature in the range of about 25° to about 80°C.

30      The present invention will now be described in greater detail by reference to the following non-limiting examples.

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EXAMPLES

All reactions were conducted under an inert atmosphere. Glassware was dried prior to use and flushed with nitrogen. Commercial materials were used when possible and the following were used as purchased: Anhydrous nickel(II) bromide, sodium bromide, anhydrous dimethylformamide, and zinc powder (-325 mesh).  
Organophosphine ligands were purchased or prepared by methods known by those of skill in the art.

Typical Experimental Procedure

Nickel(II) bromide (0.22 g, 1 mmol), the desired phosphine ligand (1.5 to 3 mmol), sodium bromide (3 g), anhydrous dimethylformamide (DMF; 15 mL), zinc powder (3 g, 45 mmol) and an aryl halide (20 mmoles) were combined under a nitrogen atmosphere and heated to 70°C for 14 to 16 hours. The mixture was cooled to ambient and analyzed by conventional chromatography techniques.  
In those cases where the DMF solvent may obscure one of the products, the reaction mixture was partitioned between aqueous ammonium chloride and ethyl acetate. The organic phase was then analyzed by normal procedures.  
Results of numerous runs with different aryl halides and different phosphine ligands are summarized in Tables I, II and III.

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Table I

Reductive Dimerization of 2-Chlorotoluene Using  
Linear Bidentate Phosphines,  $(Ph)_2P-(CH_2)_m-P(Ph)_2^*$

| 5  | Phos-               | Mmole  | [P]/<br>[Ni] <sup>1</sup> | % Convn<br>of 2-CT <sup>2</sup> | % Selectivity,<br>2,2'-Bitolyl |
|----|---------------------|--------|---------------------------|---------------------------------|--------------------------------|
|    | phine<br><u>m =</u> | Ligand |                           |                                 |                                |
| 10 | 1                   | 1.5    | 3                         | 0                               | 0                              |
|    | 2                   | 1.5    | 3                         | 24.9                            | 97.8                           |
|    | 3                   | 1.5    | 3                         | 9.4                             | 100                            |
|    | 4                   | 1.5    | 3                         | 100                             | 94.9                           |
|    | 5                   | 1.5    | 3                         | 100                             | 96.1                           |
|    | 15                  | 6      | 1.5                       | 100                             | 95.4                           |

\*All runs were carried out at 70°C for 16 hours using 1 mmol NiBr<sub>2</sub>, 30 mmol zinc, 3.0 grams of NaBr, 20 mmol of 2-CT in 15 mL DMF and ligand as noted.

20 1) Atomic ratio of phosphorus to nickel.

2) 2-CT = 2-chlorotoluene

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25 These results demonstrate that for linear bidentate phosphines of the type (iv), m must be at least 4, i.e., there must be at least 4 carbon atoms in 30 the chain between the phosphine units. Chain lengths longer than 4 carbon atoms are seen to be particularly effective.

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Table II

Reductive Dimerization of Halotoluenes to Bitolyls\*

|    | Aryl Halide     | % Convn | % Selectivity to Toluene | % Selectivity to Dimers | Expected Dimer    |
|----|-----------------|---------|--------------------------|-------------------------|-------------------|
| 5  | 2-Chlorotoluene | 100     | <0.5                     | 100                     | 98.9 <sup>1</sup> |
| 10 | 2-Bromotoluene  | 100     | 4.85                     | 95.15                   | 97.7 <sup>1</sup> |
|    | 3-Iodotoluene   | 100     | 10.8                     | 89.2                    | 80.4 <sup>2</sup> |

\*All runs were conducted at 70°C for 16 hours using  
 1 mmol NiBr<sub>2</sub>, 30 mmol zinc, 20 mmol aryl halide,  
 15 3.0 g of NaBr in DMF (15 mL). The ligand for all of  
 these runs was 2,2'-bis(diphenylphosphinomethyl)  
 -1,1'-biphenyl (BISBI; 1.5 mmol).

15      <sup>1</sup>Expected dimeric product is 2,2'-bitolyl.

20      <sup>2</sup>Expected dimeric product is 3,3'-bitolyl.

25      These results demonstrate that aryl chlorides are  
 preferred starting materials for the invention  
 reductive coupling reaction because they give the  
 desired products in high yields with very high  
 selectivity, without producing significant levels of  
 30      reduced mono-aromatic product (i.e., toluene) or  
 isomerized product (e.g., 2,3'-bitolyl).

- 20 -

Table III

The Reductive Dimerization of Substituted  
Aryl Halides to Substituted Biaryl Derivatives\*

|    | 5                          | Aryl Halide | Ligand <sup>1</sup> | % Convn | % Selectivity <sup>2</sup><br>H-Aryl Dimers | %<br>Expected<br>Isomeric<br>Dimer <sup>3</sup> |
|----|----------------------------|-------------|---------------------|---------|---|---|
| 10 | 4-Bromo-anisole            | OXYL        | 100                 | 11.4    | 88.6  | 62.7  |
| 15 | 4-Bromo-anisole            | BISBI       | 99.7                | 4.6     | 95.4  | 75.3  |
| 20 | 4-Chloro-benzotri-fluoride | OXYL        | 85.9                | 3.7     | 96.3  | 98.7  |
| 25 | 4-Chloro-benzoni-trile     | BISBI       | 100                 | 2       | 98  | 98.7  |
| 30 | 4-Chloro-benzoni-trile     | OXYL        | 100                 | 16.5    | 83.5  | 79.7  |
| 35 | Methyl-3-chloro-benzoate   | BISBI       | 100                 | 5.2     | 94.8  | 72.9  |
| 40 | Methyl-3-chloro-benzoate   | OXYL        | 100                 | 7.9     | 92.1  | 93.3  |
| 45 | 2-Chloro-aceto-phenone     | BISBI       | 88.9                | 43.2    | 56.8  | 66.6  |
|    | 2-Chloro-aceto-phenone     |             | 100                 | 9.5     | 90.5  | 54.5  |

- 21 -

Table III (Continued)

The Reductive Dimerization of Substituted  
5      Aryl Halides to Substituted Biaryl Derivatives\*

|    |   |                           | %<br>Convn | % Selectivity <sup>2</sup><br>H-Aryl Dimers | %<br>Expected<br>Isomeric<br>Dimer <sup>3</sup> |
|----|---|---------------------------|------------|---|---|
| 10 | <u>Aryl Halide</u>                        | <u>Ligand<sup>1</sup></u> |            |   |   |
|    | 4-Chloro-<br>benzalde-<br>hyde            | OXYL                      | 100        | 60  | 40  |
| 15 | 4-Chloro-<br>benzalde-<br>hyde            | BISBI                     | 100        | 19.7  | 80.3  |
| 20 | 1-Bromo-2-<br>methyl-<br>naphtha-<br>lene | BISBI                     | 28.8       | 3.6   | 96.4  |
| 25 | 1-Bromo-3-<br>fluoro-<br>benzene          | BISBI                     | 100        | <0.5  | 99.5  |
| 30 |   |                           |            |   |   |

\*All runs were carried out at 70°C for 16 hours using 1 mmol NiBr<sub>2</sub>, 30 mmol zinc, 20 mmol aryl halide, 3.0 g NaBr, 1.5 mmol of ligand in DMF (15 mL).

35    1) OXYL =  $\alpha,\alpha'$ -bis(diphenylphosphino)ortho-xylene.

          BISBI = 2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl

40    2) H-Aryl is the reduction product of the aryl halide wherein the halogen has been replaced with a hydrogen.

45    Dimers refers to all aromatic-aromatic coupling products.

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Table III (Continued)

The Reductive Dimerization of Substituted  
Aryl Halides to Substituted Biaryl Derivatives\*

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- \*3) Expected isomeric dimer of:  
10      4-bromoanisole is 4,4'-dimethoxybiphenyl;  
15      4-chlorobenzotrifluoride is 4,4'-bis(trifluoro-  
          methyl)biphenyl;  
20      4-chlorobenzonitrile is 4,4'-dicyanobiphenyl;  
          methyl-3-chlorobenzoate is the dimethyl ester of  
          3,3'-diphenyldicarboxylic acid;  
25      2-chloroacetophenone is 2,2'-diacetyl biphenyl;  
          4-chlorobenzaldehyde is 4,4'-diphenyldicarbox-  
          aldehyde;  
30      1-bromo-2-methylnaphthalene is 2,2'-dimethyl-  
          1,1'-binaphthyl; and  
          1-bromo-3-fluorobenzene is 3,3'-difluorobiphenyl.

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The data in Table III demonstrate that a wide variety of functional groups are compatible with the invention process.

The invention has been described in detail with  
5 particular reference to preferred embodiments thereof,  
but it will be understood that variations and  
modifications can be effected within the spirit and  
scope of the invention.

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Claims

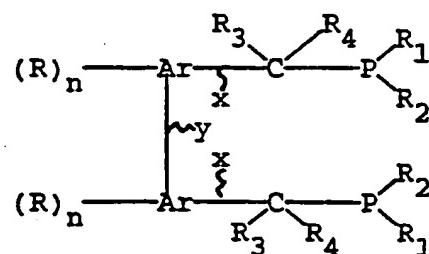
We Claim:

5           1. A method for coupling aryl and heteroaryl monohalides having 4 to 20 carbon atoms to produce biaryl or hetero-biaryl compounds, said method comprising contacting said monohalide with a catalytic combination comprising:

- 10
- 15           (I) an anhydrous nickel compound, wherein the ratio of gram atoms of nickel to moles of monohalide is in the range of about 0.0001 up to 0.5;
- 20           (II) at least one bidentate phosphorus-containing ligand selected from the group consisting of

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(i)



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wherein each Ar is independently selected from aromatic ring compounds having 4 up to 20 carbon atoms;

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the x bonds and the y bonds are attached to adjacent carbon atoms on the ring structures;

- 25 -

each R, when present as a substituent, is independently selected from alkyl, aryl,

5           -F, -NR'<sub>2</sub>, -CN, -CHO, -OR', -OCO-R',

10           -COO-R', -C<sup>O</sup>-R', -SO<sub>2</sub>-R', -SO<sub>3</sub>R',

or -NR'COR':

15           wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms;

n is an integer in the range of 0-4 where Ar is phenyl; 0-6 where Ar is naphthyl; and 0-8 where Ar is phenanthryl or anthracenyl;

20           each R<sub>1</sub> and R<sub>2</sub> is independently selected from alkyl, aryl, aralkyl, alkaryl or cycloaliphatic radicals, or substituted derivatives thereof wherein substituted derivatives include ethers, amines, amides, sulfonic acids, esters, hydroxyl groups and alkoxy groups;

25           each R<sub>3</sub> and R<sub>4</sub> is independently selected from hydrogen and the R<sub>1</sub> substituents;

30           each of the above alkyl groups or moieties is straight or branched chain of 1-20 carbon atoms;

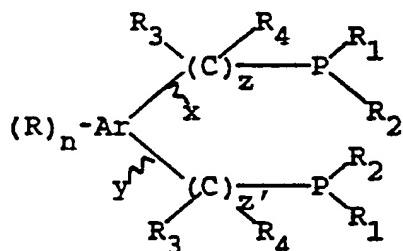
35           each aryl group contains 4-20 ring carbon atoms; and

40           each cycloaliphatic group contains from 4-8 ring carbons;

- 26 -

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(ii)

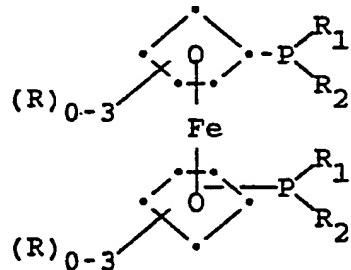


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wherein Ar, x, y, R, n, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are each as defined above, and each of z and z' can independently vary between 0 and 4, with the proviso that z+z' is at least 2;

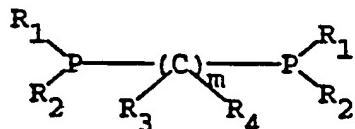
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(iii)



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(iv)



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wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined above; and m is a whole number which can vary from 4 up to 8;

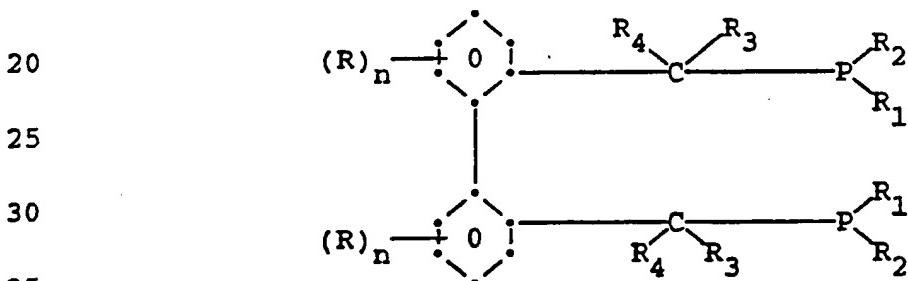
as well as mixtures of any two or more thereof; wherein the amount of ligand is in the range of about 0.5 up to 20 moles per gram atom of nickel; and

- 27 -

(III) at least one reducing metal selected from  
the group consisting of zinc, magnesium and  
manganese; wherein the molar ratio of  
reducing metal to reactant monohalide falls  
5 in the range of about 0.01 up to 20:1;

10 wherein said contacting is carried out in  
the presence of a polar, aprotic solvent at  
a temperature in the range of 0 up to 250°C  
15 for a time sufficient to form said biaryl or  
heterobiaryl compounds.

2. The method in accordance with Claim 1  
wherein said bidentate ligand has the  
15 structural formula:



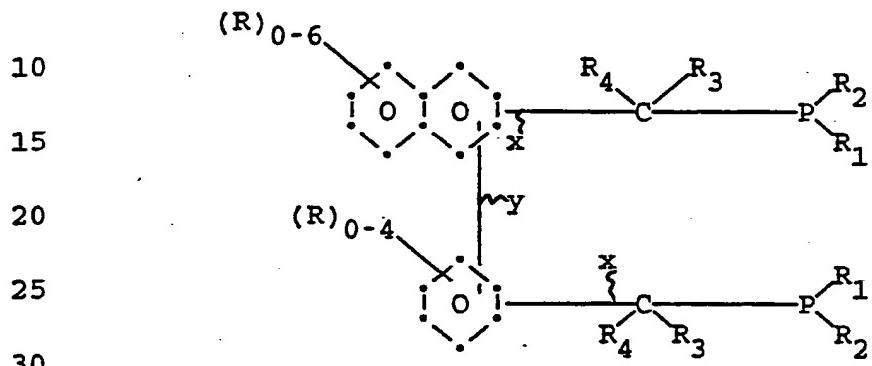
40 wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and n are as  
defined above.

3. The method in accordance with Claim 2  
wherein said bidentate ligand is selected  
from the group consisting of:  
45 2,2'-bis(diphenylphosphinomethyl)-1,1'-  
biphenyl;  
2,2'-bis(dibenzylphosphinomethyl)-1,1'-  
biphenyl;  
50 2,2'-phenylbenzylphosphinomethyl)-1,1'-  
biphenyl; and

- 28 -

*2,2'-bis(diisobutylphosphinomethyl)-1,1'-biphenyl.*

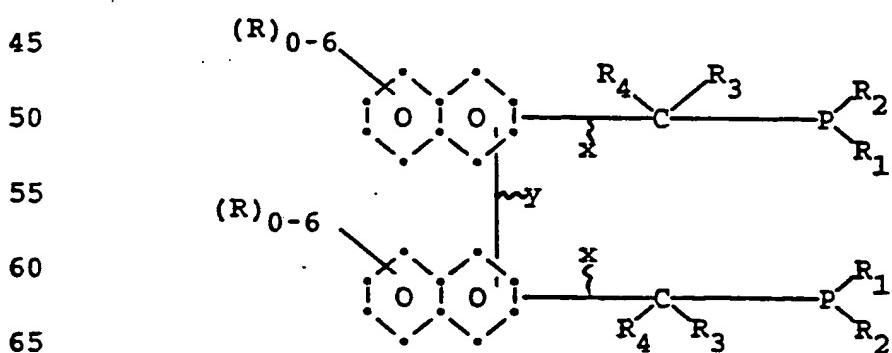
4. The method in accordance with Claim 1 wherein said  
5 bidentate ligand has the structural formula:



wherein R,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ , x and y are as defined above.

- 35 5. The method in accordance with Claim 4 wherein said bidentate ligand is 2-(diphenylphosphino-methyl)-1-[2-(diphenylphosphinomethyl)phenyl]-naphthalene.

- 40 6. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:

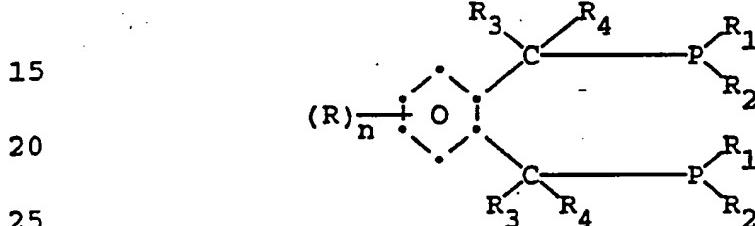


- 29 -

wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, x and y are as defined above.

7. The method in accordance with Claim 6 wherein said bidentate ligand is 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl.
- 5
8. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:

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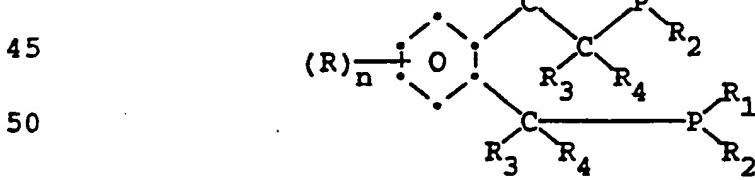
wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and n are as defined above.

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9. The method in accordance with Claim 8 wherein said bidentate ligand is  $\alpha,\alpha'$ -bis(diphenylphosphino)ortho-xylene.

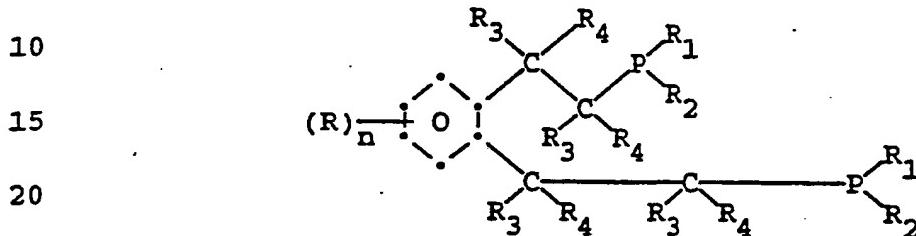
10. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:

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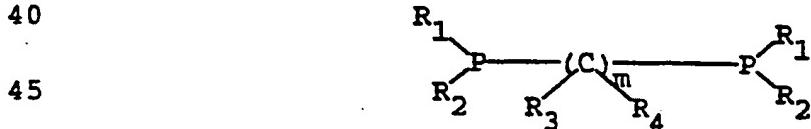
- 30 -

11. The method in accordance with Claim 10 wherein said bidentate ligand is  $\alpha,\beta'$ -bis(diphenylphosphino)-2-ethyltoluene.
- 5 12. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:



wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and n are as defined above.

- 30 13. The method in accordance with Claim 12 wherein said bidentate ligand is 1,2-bis[2-(diphenylphosphino)ethyl]benzene.
- 35 14. The method in accordance with Claim 1 wherein said bidentate ligand is 1,1'-bis(diphenylphosphino)ferrocene.
15. The method in accordance with Claim 1 wherein said bidentate ligand has the structural formula:



50 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined above; and wherein m is a whole number which can vary from 4 up to 8.

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16. The method in accordance with Claim 15 wherein said bidentate ligand is selected from the group consisting of:

5           1,4-bis(diphenylphosphino)butane,  
              1,5-bis(diphenylphosphino)pentane,  
              1,6-bis(diphenylphosphino)hexane,

as well as mixtures of two or more thereof.

- 10           17. The method in accordance with Claim 1 wherein said catalytic combination further comprises at least one bidentate ligand containing at least one nitrogen atom as part of an aromatic ring structure.

- 15           18. The method in accordance with Claim 17 wherein said bidentate ligand containing at least one nitrogen atom is selected from 2,2'-bipyridine, a C<sub>1</sub> up to C<sub>6</sub> dialkylamino pyridine, phenanthroline or 2-picolinic acid.

- 20           19. The method in accordance with Claim 1 wherein said reducing metal is zinc.

- 25           20. The method in accordance with Claim 1 wherein the nickel compound is nickel chloride.

- 30           21. The method in accordance with Claim 1 wherein at least 0.1 moles per gram atom of nickel of an inorganic salt is added as a promoter.

- 35           22. The method in accordance with Claim 21 wherein the inorganic salt is selected from the group consisting of: an alkali metal iodide, an alkali

- 32 -

metal bromide, an alkali metal chloride, as well as mixtures of any two or more thereof.

23. The method in accordance with Claim 1 wherein the  
5 aprotic solvent is N,N-dimethylacetamide.
24. The method in accordance with Claim 1 wherein the  
aprotic solvent is N,N-dimethylformamide.
- 10 25. The method in accordance with Claim 1 wherein the  
aprotic solvent is 1-methyl-2-pyrrolidinone.
26. The method in accordance with Claim 1 wherein the  
monohalide has the formula:

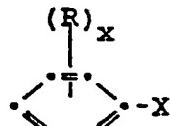
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(I)

wherein one or more of the carbon atoms of the benzene ring in formula (I) is optionally replaced by N;

wherein X is a halogen selected from the group consisting of Cl, Br and I;

40 R is a monovalent radical selected from alkyl,  
aryl, -F, -NR'<sub>2</sub>, -CN, -CHO, -OR',  
-OCO-R', -COO-R', -C(=O)-R', -SO<sub>2</sub>-R', -SO<sub>3</sub>-R',  
45 or -NR'COR':

- 33 -

wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms, and x is an integer having values of 0 to 4 with the proviso that no more than one R is in a position ortho to the X-containing ring carbon atom.

- 5                    27. The method according to Claim 26 wherein X is Cl.
- 10                  28. The method according to Claim 27 wherein said monohalide is selected from the group consisting of:
- 15                  2-chlorotoluene,  
                      2-chloropyridine,  
                      4-fluoro-2-chlorotoluene,  
                      2-chlorobenzyl methyl ether,  
                      2-chlorobenzyl ethyl ether,  
                      4-(N-ethyl-N-acetyl)-2-chlorotoluene,  
                      6-(N-ethyl-N-acetyl)-2-chlorotoluene,  
20                  4-chlorotoluene,  
                      4-chloroanisole,  
                      2-chlorobenzyl(2-methoxy)ethyl ether,  
                      as well as mixtures of any two or more thereof.
- 25                  29. A method as claimed in Claim 26 wherein R is methyl and x is 1.
- 30                  30. A method as claimed in Claim 1 wherein the temperature is from about 25°C to about 120°C.
- 35                  31. The method in accordance with Claim 30 wherein the ratio of gram atoms of nickel to moles of monohalide falls in the range of about 0.01 up to 0.2:1; the amount of bidentate

- 34 -

phosphorus-containing ligand falls in the range of about 1 up to 10 moles per gram atom of nickel; and the molar ratio of reducing metal to reactant monohalide falls in the range of about 0.2 up to 10:1.

5

32. The method in accordance with Claim 30 wherein the ratio of gram atoms of nickel to moles of monohalide falls in the range of about 0.03 up to 10 0.1:1; the amount of bidentate phosphorus-containing ligand falls in the range of about 1 up to 5 moles per gram atom of nickel; and the molar ratio of reducing metal to reactant monohalide falls in the range of about 0.4 up to 15 5:1.

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33. A catalytically active combination comprising:

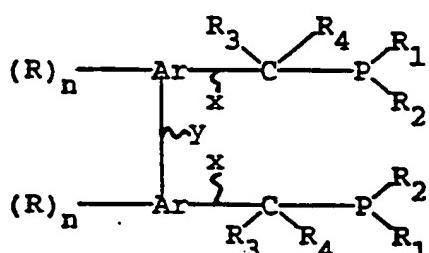
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(I) an anhydrous nickel compound,

25 (II) at least one bidentate phosphorus-containing 30 ligand selected from the group consisting 35 of

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(i)



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wherein each Ar is independently selected from aromatic ring compounds having 6 up to 14 carbon atoms;

- 35 -

the x bonds and the y bonds are attached to adjacent carbon atoms on the ring structures;

5 each R, when present as a substituent, is independently selected from alkyl, aryl, -F, -NR'<sub>2</sub>, -CN, -CHO, -OR', -OCO-R',

10 -COO-R', -C<sup>O</sup>-R', -SO<sub>2</sub>-R', -SO<sub>3</sub>-R', or -NR'COR':

15 wherein R' is a hydrocarbyl or heteroaryl radical having up to 20 carbon atoms;

20 n is an integer in the range of 0-4 where Ar is phenyl; 0-6 where Ar is naphthyl; and 0-8 where Ar is phenanthryl or anthracenyl;

25 each R<sub>1</sub> and R<sub>2</sub> is independently selected from alkyl, aryl, aralkyl, alkaryl or cycloaliphatic radicals, or substituted derivatives thereof wherein substituted derivatives include ethers, amines, amides, sulfonic acids, esters, hydroxyl groups and alkoxy groups;

30 each R<sub>3</sub> and R<sub>4</sub> is independently selected from hydrogen and the R<sub>1</sub> substituents;

35 each of the above alkyl groups or moieties is straight or branched chain of 1-20 carbons;

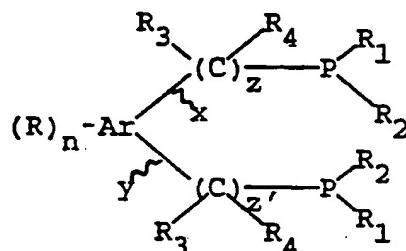
each aryl group contains 4-20 ring carbons; and

- 36 -

each cycloaliphatic group contains from 4-8 ring carbons;

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(ii)

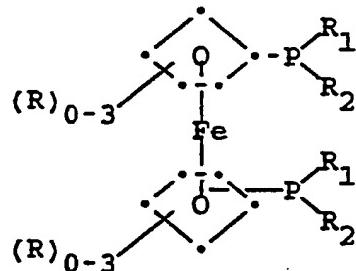


25  
30

wherein Ar, x, y, R, n, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are each as defined above, and each of z and z' can independently vary between 0 and 4, with the proviso that z+z' is at least 2;

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(iii)

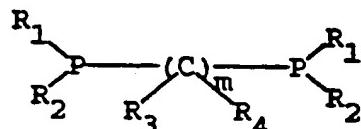


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wherein R, R<sub>1</sub>, and R<sub>2</sub> are as defined above; and

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(iv)



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wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined above; and wherein m is a whole number which varies from 5 up to 8;

- 37 -

as well as mixtures of any two or more of said type (i), (ii), (iii), or (iv) organophosphines; and

5 (III) at least one reducing metal selected from the group consisting of zinc, magnesium and manganese;

10 wherein the amount of bidentate phosphorus-containing ligand falls within the range of 0.5 up to 20 moles per gram atom of nickel; and wherein the amount of reducing metal falls within the range of about 1 up to 1000 moles per mole of nickel.

15

## INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/05218

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC<sup>5</sup> C 07 B 37/04, C 07 C 15/14, 25/18, 43/164, 43/205,  
IPC<sup>5</sup> C 07 D 213/22, C 07 C 1/26, 17/26, 41/30, C 07 D 213/127

## II. FIELDS SEARCHED

Minimum Documentation Searched <sup>7</sup> -

| Classification System   | Classification Symbols                                   |
|---|--|
| IPC <sup>5</sup>  | C 07 B 37/00, C 07 C 1/00, C 07 C 15/00,<br>B 01 J 31/00 |
| Documentation Searched other than Minimum Documentation<br>to the Extent that such Documents are Included in the Fields Searched <sup>8</sup> |  |

## III. DOCUMENTS CONSIDERED TO BE RELEVANT\*

| Category <sup>9</sup> | Citation of Document, <sup>10</sup> with indication, where appropriate, of the relevant passages <sup>11</sup>   | Relevant to Claim No. <sup>12</sup> |
|-----------------------|--|-------------------------------------|
| A                     | EP, A, 0012201 (UNION CARBIDE))<br>25 June 1980, see claims; page 4,<br>lines 17-21<br>--  | 1-33                                |
| A                     | The Journal of Organic Chemistry,<br>vol. 51, no. 14, 11 July 1986<br>American Chemical Society (US)<br>I. Colon et al.: "Coupling of aryl<br>chlorides by nickel and reducing metals"<br>pages 2627-2637<br>(cited in the application)<br>--  | 1-33                                |
| A                     | Bulletin of the Chemical Society of Japan,<br>vol. 57, no. 7, July 1984 (JP)<br>K. Takagi et al.: "Ni(0)-trialkyl-<br>phosphine complexes. Efficient homo-<br>coupling catalyst for aryl, alkenyl,<br>and heteroaromatic halides"<br>pages 1887-1890,<br>see the whole article<br>(cited in the application) | 1-33                                |

\* Special categories of cited documents: <sup>10</sup>

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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## IV. CERTIFICATION

Date of the Actual Completion of the International Search

13th March 1990

Date of Mailing of this International Search Report

12 APR 1990

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Mme N. KUIPER

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 89/05218 -2-

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC<sup>4</sup> : B 01 J 31/26, //C 07 C 49/784, 69/76, 255/51

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

| Classification System | Classification Symbols |
|-----------------------|------------------------|
| IPC <sup>4</sup>      |                        |

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched \*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT\*

| Category * | Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup> | Relevant to Claim No. <sup>13</sup> |
|------------|--|-------------------------------------|
|            |  |                                     |

\* Special categories of cited documents: <sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "P" document published prior to the international filing date but later than the priority date claimed

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Date of the Actual Completion of the International Search

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International Searching Authority

Signature of Authorized Officer

EUROPEAN PATENT OFFICE

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 8905218  
SA 32904

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/04/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) |         | Publication<br>date |
|---|---------------------|----------------------------|---------|---------------------|
| EP-A- 0012201                             | 25-06-80            | US-A-                      | 4263466 | 21-04-81            |